rejected in the outstanding Official Action, which are directed to an alkaline salt of proton pump inhibitors.

Applicants hereafter respectfully submit that the presently pending claims are not only not anticipated by Cui et al. (Chinese Patent Publication No. 1367172, Abstract only), but also not obvious over Cui et al. in view of Kohl (US 6,410,569).

1. Rejection of Claims 1-5 and 7 under 35 U.S.C. §102(b)

The Official Action states in relevant part that claims 1-5 and 7 are rejected under 35 U.S.C. §102(b) as being anticipated by Cui et al. (Abstract only).

As the basis of the rejection, the Official Action states that:

> Cui et al. teach magnesium salts of [(substituted pyridyl)methyl]sulfinyl-1H-benzimidazole derivatives, including pantoprazole, and that they can be used as proton pump inhibitors. Cui et al. teach the preparation of these compounds involves dissolving the [(substituted pyridyl)methyl]sulfinyl-1H-benzimidazole compound in alkaline aqueous solution adjusted to pH 9-13, followed by the drop-wise addition of a water-soluble magnesium salt solution (e.g., $MgCl_2$ or $Mg(NO_3)_2$) and the precipitated collected.
> The instant Specification discloses the compound of formula pantoprazole$^-$ $Mg_2^+H_2O$ (the elected species) as being prepared by the same reaction. Absent evidence to the contrary, the compound formed by the reaction taught by Cui et al. would have produced the same compound disclosed in the instant Specification and Claims.
> It is noted that *In re Best* (195 USPQ 430) and *In re Fitzgerald* (205 USPQ 594) discuss the support of rejections wherein the prior art discloses subject matter, which there is reason to believe inherently includes functions that are newly cited, or is identical to a product instantly claimed. In such a situation the burden is shifted to the applicants to "prove that subject matter to be shown in the prior art does not posses the characteristic relied on" (205 ISPQ 594, second column, first full paragraph) There is no requirement that a person of ordinary skill in the art ... ... Toro Co. v. Deere & Co., 355 F.3d 1313, 1320, 69 USPQ2d 1584, 1590 (Fed. Cir. 2004)("[T]he fact that a characteristic is a necessary feature or result of a prior-art embodiment (that is itself sufficiently described and enabled) is enough for inherent anticipation, even if that fact was unknown at the time of the prior invention").

In this regard, applicants respectfully submit that the Abstract of Cui et al., taken alone as the Examiner does in this rejection, does not provide a sufficient disclosure to fully describe and enable the presently pending claims, even under a standard of inherent anticipation, as required by *Toro Co. v. Deere & Co. Id.* Nevertheless, for the sake of convenience and in order to expedite the prosecution for the present application, applicants have obtained the full text of Cui et al. (Chinese Patent Publication No. 1367172) and reviewed it to correctly understand what Cui et al. disclose in the entire reference. Copies of the text, along with its English translation, are herewith enclosed as Exhibit A.

Based on the disclosure in the full text of Cui et al., applicants respectfully traverse this rejection. The test for anticipation is whether each and every element as set forth is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987); MPEP §2131. The identical invention must be shown in as complete detail as is contained in the claim. *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989); MPEP §2131. The elements must also be arranged as required by the claim. *In re Bond*, 15 USPQ2d 1566 (Fed. Cir. 1990). Moreover, the rule of law requires that the Examiner must consider a reference in its entirety in determining the scope and content of the reference. *W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540, (Fed. Cir 1983), *cert. denied*, 469 U.S. 851 (1984). Thus, the Examiner must acknowledge any disclosure in the reference that teaches away from the present invention. *Id.*

In this regard, Cui et al., both in the abstract and in the full specification, fail to

disclose each and every element of the subject matter of the presently pending claims, either expressly or inherently, as required by *Verdegaal Bros. v. Union Oil Co. of California*, and thus do not anticipate the presently pending claims.

Presently claimed subject matter

The presently claimed subject matter, in particular the presently pending independent claim 1, is directed to a pharmacologically compatible metal salt of a pyridin-2-ylmethylsulphinyl-1H-benzimidazole with H+/K+-ATPase-inhibitory activity where at least one positive charge equivalent of a metal ion is counterbalanced by a hydroxyl ion, namely "Pantoprazole^{-}OH^{-}Mg^{2+}H$_2$O" as the elected species.

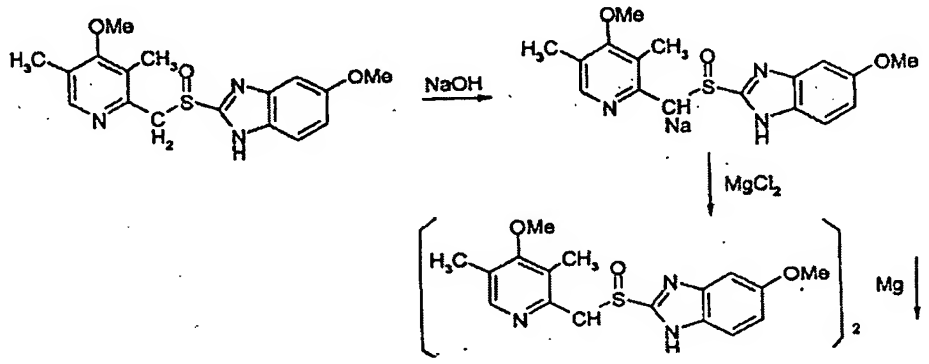
As describe in the specification, substituted benzimidazoles referred as proton pump inhibitors (PPI), show a kind of sensitivity to acids, which makes them difficult to handle in neutral and especially in acid environments. In order to overcome this disadvantage, some efforts have been made in the past, for example by choosing specific cations, which led to improved stability properties of the compounds. In the present application, the inventors have improved the stability of substituted benzimidazoles by incorporating alkaline reaction "moieties" in to the compound itself.

Disclosure of Cui et al.

Cui et al. do not teach anything that would anticipate the subject matter of the pending claims. Applicants draw the Examiner's attention first to the disclosure at page 2 of Cui et al., which directly points to a pure magnesium salt of the substituted benzimidazole (i.e., omeprazole) in contrast to the presently claimed subject matter

(see, page 6 of the English translation):

> Said process for preparing a magnesium salt of a compound of the type of [(substituted pyridyl)methyl]sulfinyl-1H-benzimidazol of the present invention is as follows, dissolving the [(substituted pyridyl)methyl]sulfinyl-1H-benzimidazol compound into an alkaline aqueous solution, making the pH value of the solution to 9-13, preferably be pH 9-10, then adding into the aqueous solution by dripping a calculated amount of a water-soluble magnesium salt solution, having it thoroughly precipitated and collecting the precipitate so as to obtain the corresponding magnesium salt of the [(substituted pyridyl)methyl] sulfinyl-1H-benzimidazol compound. By taking the omeprazole magnesium salt as an example its reaction process is as follows:



Second, applicants draw the Examiner's attention to another disclosure at page 3, 3rd paragraph of Cui et al., which teaches a <u>ratio of PPI to magnesium of 1 to 0.5</u>

(see, page 7, 2nd paragraph of the English translation):

> Since in the above-mentioned magnesium salt of the [(substituted pyridyl)methyl] sulfinyl-1H-benzimidazol compound, the theoretically calculated value of molar ratio of the [(substituted pyridyl)methyl]sulfinyl-1H-benzimidazol compound to magnesium ions in the salification is 1:0.5. Therefore, during said salification of the [(substituted pyridyl)methyl]sulfinyl-1H-benzimidazol compound and magnesium salt in the alkali aqueous solution, if the added amount of magnesium is less than the calculated amount, it will certainly lead to the incomplete salification; while an excess addition of magnesium will lead to excess production of magnesium hydroxide, which also increases the complication and difficulties of the aftertreatment operation and influences the yield and purity of the required product. The experimental results have shown that, by giving considerations to the two cases, a molar ratio of 1:0.45 to 0.55 of the [(substituted pyridyl)methyl] sulfinyl-1H-benzimidazol compound to the magnesium ions is

generally used as the calculated amount of the dripping aqueous solution mentioned above, which has achieved a satisfactory result.

From this disclosure, it is very clear that Cui et al. do not disclose a compound as presently claimed. The recommended and used ratio of PPI to Mg of 2 : 1 cannot lead to a compound having a ratio of PPI to Mg of 1 : 1, as required for example for the elected species of the presently pending claims.

This is further confirmed by the results of the examples of Cui et al., where almost all of the used PPI is recovered from the reaction mixture. If a compound with an 1:1 ratio of PPI to Mg should have been formed during the described reactions, at maximum only 50% of the used PPI should have been recovered in the precipitate. However, the amounts of PPI precipitated in the Examples of Cui et al. are mostly over 90%. The following overview summarizes the relevant ratios as used in the examples of Cui et al.:

Ex.	PPI / mmol		NaOH / mmol	Mg-salt / mMol	PPI : Mg	Amount of PPI precipitated %
1	S-Ome	14,5	18,76	7,23	2 : 1	98.2
2	S-Ome	14,5	28	7,23	2 : 1	85.0
3	S-Ome	14,5	18,2	7,23	2 : 1	99.1
4	S-Ome	14,5	n.a.	7,23	2 : 1	98.7
5	R/S-Ome	14,5	n.a.	7,23	2 : 1	n.a.
6	Panto	14,2	n.a.	7,08	2 : 1	n.a.
7	S-Ome	86,8	n.a.	43,4	2 : 1	99.1
8	Lanso	13,5	n.a.	6,79	2 : 1	n.a.
9	R-Ome	14,5	n.a.	7,23	2 : 1	98.1

n.a. = not available

Beside the PPI : Mg ratio, there exists another disclosure that the teaching of Cui et al. does not inherently anticipate the subject matter of the presently pending claims. Applicants draw the Examiner's attention in this regard to the disclosure of Cui et al. regarding the ratio between PPI and free acid. In all of the described examples of Cui

et al., the free acid of the PPI is used, which indicates that a hydrogen atom is connected to one of the nitrogen atoms of the benzimidazole moiety of the molecule. In contrast to the disclosed reaction scheme of Cui et al., it is well known that the deprotonation occurs at the benzimidazole moiety of the molecule and not at the methylene group of the sulfinylpyridyl-methyl moiety. One stoichiometric equivalent of sodium hydroxide is necessary to withdraw this hydrogen atom from the benzimidazole moiety.

Different from the teaching in Cui et al., the examples of the present application always start from the sodium salt of the PPI, thus omitting the first step of deprotonation of the benzimidazole moiety as required by Cui et al. (withdrawal of hydrogen atom from one of the benzimidazole nitrogens).

Lastly, applicants draw the Examiner's attention to the disclosure of the physical data provided for example 1 of Cui et al., especially the IR data. For comparison purposes, a collection of IR spectra of different compounds is herewith enclosed as Exhibit B. The collection shows from top to bottom the IR-spectra of (pantoprazole)$_2$Mg 2xH_2O (as described in the Kohl reference), *rac-(*pantoprazole) OH Mg 1xH_2O (example 1 of the present application), *(S)-(*pantoprazole) OH Mg 1xH_2O (examples 2 and 11 of the present application) and (pantoprazole)$_3$ OH Mg_2 4xH_2O (example 4 of the present application).

From this comparison it is immediately evident that the IR spectra of the latter three compounds show additional vibrations at around 3700 cm^{-1}, 2370 cm^{-1} and 2345 cm^{-1} which refer to the OH-ion. The IR-spectra of (pantoprazole)$_2$Mg 2xH_2O is plain in these areas of the IR-spectra. Although Cui et al. only provide IR-data for

$(omeprazole)_2Mg$ (example 1), and although omeprazole has some different substituents at the benzimidazole and pyridyl moieties than pantoprazole, these differences can not have a high influence with respect to the areas around 3700 cm^{-1} and between 2300 and 2400 cm^{-1}. The given data in Cui et al. for $(omeprazole)_2Mg$ "FT-IR(KBr)cm^{-1}: 2997.7(Ar), 2949.6, 2835.2(-CH_3, -CH_2-), 1616.2, 1570.0, 1271.2, 1155.2, 1077.6, 839.0" are very similar to the IR spectra of $(pantoprazole)_2$ Mg $2xH_2O$ from the Kohl reference and clearly indicate that no OH anion is present.

In view of the above mentioned facts, it is obvious that Cui et al. only describe $(PPI)_2Mg$ compounds. None of the examples of Cui et al. provide any teachings or suggestions which would render the subject matter of the pending claims as anticipated, either expressly or inherently. Accordingly, applicants respectfully request the Examiner to reconsider and withdraw this rejection of pending claims 1-5 and 7.

2. Rejection of Claims 1-5, 7, 13 and 14 under 35 U.S.C. §103(a)

The Examiner rejected claims 1-5, 7, 13 and 14 under 35 U.S.C. §103(a) as being unpatentable over Cui et al. in view of Kohl (US 6,410,569).

As the basis of the rejection, the Official Action states in relevant part:

> The teachings of Cui et al. have been presented supra.
> Kohl teaches a pharmaceutical composition of pantoprazoel magnesium dehydrate and its use in a method of treating amenable disorders of the stomach or intestine. See col.4, claims 1,2 and 8. Kohl teaches the increased stability of the magnesium salts of pantoprazole. See col.1, last paragraph. Indeed, Kohl presents evidence of the stability of the magnesium pantoprazole salt that is comparable to that presented in the instant Specification. See Kohl ref. Col.3, 1st paragraph, and instant Specifcation, page 5, lines 14-18.
> One of ordinary skill in the art at the time of the invention would have known that proton pump inhibitors were useful for the treatment of disorders of the gastrointestinal system and that effective compounds must be formulated with pharmaceutically acceptable auxiliary agents (e.g. carriers, diluents,

> disintegrants, etc.). The artisan would have found it obvious to combine the teachings of the two references cited above, motivated by the need to make pharmaceutical compositions of pantoprazole, having greater stability, for use in treating gastrointestinal disorders.
> A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. (*In re Opprecht* 12 USPQ 2d 1235, 1236 (Fed. Cir. 1989); *In re Bode* 193 USPQ 12 (CCPA) 1976). In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a). From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole is prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicants respectfully traverse this rejection. To establish a *prima facie* case of obviousness, the PTO must satisfy three requirements. First, as the U.S. Supreme Court very recently held in *KSR International Co. v. Teleflex Inc. et al.*, Slip Opinion No. 04–1350, 550 U. S. __ (April 30, 2007), "a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions. ...it [may] be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. ...it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does... because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known." (*KSR*, *supra*, slip opinion at 13-15.) Second, the

proposed modification of the prior art must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. *Amgen Inc. v. Chugai Pharm. Co.*, 18 USPQ2d 1016, 1023 (Fed. Cir. 1991). Lastly, the prior art references must teach or suggest all the limitations of the claims. *In re Wilson*, 165 USPQ 494, 496 (C.C.P.A. 1970).

Applicants hereby incorporate by reference in its entirety the discussion in Section 1 above regarding the presently claimed subject matter, the disclosure of the full text of the Cui et al. reference, and the differences between the two.

In summary, Cui et al. teach a synthesis path for pure PPI magnesium salts $(PPI)_2Mg$. In contrast the presently claimed subject matter is directed to a pharmacologically compatible metal salt of a pyridin-2-ylmethylsulphinyl-1H-benzimidazole with H+/K+-ATPase-inhibitory activity where at least one positive charge equivalent of a metal ion is counterbalanced by a hydroxyl ion, namely "Pantoprazole$^-$ $OH^-Mg^{2+}H_2O$" as the elected species.

Kohl does not remedy the deficiencies of Cui et al.

Kohl discloses magnesium pantoprazole dihydrate which is prepared by reacting pantoprazole sodium sesquihydrate with magnesium dichloride hexahydrate in purified water, centrifuging, washing and drying the precipitated solid (see, column 2, lines 45 – 67 and the Examples). The reaction is performed without the use of any further hydroxide ions being present in the solution. The same situation applies to the alternative synthesis route as described in the paragraph bridging columns 3 and 4 of Kohl. Additionally, the melting point of pantoprazole magnesium dihydrate as disclosed

in Kohl is higher than the melting point of example 1 of the present application, magnesium pantoprazole hydroxyl monohydrate (194-196°C vs. 184-187°C, page 7 top). Accordingly, the compound as disclosed in Kohl is different from the compounds as described and claimed in the present application.

Further, applicants note that there are no major differences between the teachings of Cui et al. and Kohl with respect to the final compounds. Both references describe PPI magnesium salts whereby Kohl is limited to pantoprazole as PPI the and further defines the obtained compound to be a dihydrate. However, the ratio between the PPI and Mg in the final products is identical.

The main difference with respect to the synthesis paths is that Cui et al. start from the free acid form of the benzimidazoles and Kohl starts from the sodium salt. With respect to the alternative route of Kohl, the reaction is performed in a non-aqueous medium directly with magnesium methanolate (paragraph bridging columns 3 and 4). Since both teachings lead to almost identical compounds, Kohl fails to remedy the deficiencies of Cui et al. There is no guidance to a person of ordinary skill in the art to arrive at the presently claimed compounds, thus providing PPI compounds with an increased stability, based on the Cui et al. and Kohl references.

Accordingly, Cui et al., taken alone or in combination with Kohl, does not teach or suggest the subject matter of the pending claims. As such, applicants respectfully request the Examiner to reconsider and withdraw the rejection of pending claims 1-5, 7, 13, and 14.

CONCLUSION

Based upon the above remarks, the presently claimed subject matter is believed to be novel and patentably distinguishable over the prior art of record. The Examiner is therefore respectfully requested to reconsider and withdraw the outstanding rejections and allow all pending claims. Favorable action with an early allowance of the claims pending in this application is earnestly solicited.

The Examiner is welcomed to telephone the undersigned attorney if she has any questions or comments.

Respectfully submitted,

THE NATH LAW GROUP

Date: March 13, 2008

By: _____

Gary M. Nath
Reg. No. 26,965
Joshua B. Goldberg
Reg. No. 44,126
Customer No. 34375

THE NATH LAW GROUP
112 S. West Street
Alexandria, VA 22314
Tel: (703) 548-6284
Fax: (703) 683-8396
GMN:JBG:MSK\27133UROA.doc